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14. ABSTRACT

Conventional chemotherapy with cell killing en mass often targets mitotic cells with less specificity, which likely leads to undesirable side effect. Knowing specific molecular defects in cancer cells has led to discover new chemotherapeutic agents. Thus, combined agents targeting different defected pathways in cancer cells have a better chance to eradicate tumor completely. Thus, to achieve a cure, a comprehensive targeting strategy needs to be implemented. In addition, improved methods for monitoring drug delivery and tumor response in a nearly real-time manner should offer a safe and effective treatment. This project carried out by a team of chemist, radiologist, and molecular tumor biologist is to develop a novel drug delivery system with new small molecular therapeutic agents assisted with new imaging probe is expect to bring a new frontier for prostate cancer (PCa) management. Our objective is to develop dendrimer-based theranostic agent with prostate cancer specificity and positron emission tomography imaging capability that can prevent the early onset of PCa metastasis or delay the progression of metastasis. The mission of my project is to design small peptide derived from tumor suppressor DAB2 family as therapeutic agent and examine its biology activities.

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INTRODUCTION

Targeted therapy now becoming an active research area of cancer therapy is expected to achieve a better efficacy for individual patient. In order to target prostate cancer (PCa) specifically, we have discovered a unique cell permeable peptide with PCa targeting specificity (1-3). In addition, we also studied a potent tumor suppressor-DAB2IP in PCa and identified the functional domain (4). We were able to demonstrate the tumor suppressive function using synthetic peptide corresponding the functional domain (4).
To generate molecular medicine combining both targeting peptide and therapeutic peptide, we proposed to use dendrimer nanoparticle platform as a drug delivery vehicle to deliver therapeutic peptide to target PCa. In addition, we will equip PET tracer to make this platform to become a theranostic agent. Our major activities are constructing dendrimer conjugated with therapeutic peptide, determining the mechanism of action and preparing chelator for conjugating PET tracer and dendrimer.

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KEYWORDS

Prostate cancer, targeted therapy, cell permeable peptide, dendrimer, PET, DAB2IP

ACCOMPLISHMENTS

A. PROJECT ACCOMPLISHMENTS

Goal 3: To evaluate the therapeutic efficacy using various pre-clinical models.

- Demonstrate tumorstatic effect of dendrimer conjugates at 50 mg/kg using subcutaneous model.

  During this year, we have examined this most potential dendrimer conjugate (CSIV-81) using xenograft model. Last year, we have examined LAPC4 KD tumor using 10 mg/kg and could not find any change of the target-pAKT. We conclude this model may not be suitable because it is a very slow growing model; AKT may not be the key factor for the survival of this model. We therefore employed another subcutaneous tumor model-PC3 and implanted minipump to deliver this agent once tumors became

palpable. In our first trial (Appendix Figure 1) using 10 mg/kg daily dosage for 7 days, we found this agent failed to inhibit tumor growth. We have further analyzed biochemical targets (pAKT) in these tumors using western blot and revealed no significant change as well (Appendix Figure 3: Upper panel).

We then decided to increase the dosage to 50 mg/kg that is close to the maximal tolerant dose. However, due to issue of scale-up drug synthesis, we have to postpone our second trail for few months. Nevertheless, the result is quite encouraging, a significant tumor inhibitory effect (Appendix Figure 2) was observed in this treatment protocol. Consistently, a reduced pAKT levels were observed in tumors treated with this dose of CSIV-81 (Appendix Figure 3 Lower panel)

This project was carried out by a senior prostdoctor who is able to learn experimental therapy for his new skill set. He is able to master animal model, pharmacokinetics, drug delivery and target validation. These experiences along with his other accomplishments let him to secure a faculty position in a research institute.

Currently, we are planning to examine different model, formulate with treatment schedule and develop theranostic agent prior to submitting peer-reviewed manuscript.

B. OTHER ACHIEVEMENTS

N/A

IMPACT

This project combines the recent advances in PCa research from three different laboratories to develop a new molecular medicine. The goal of this project is to construct dendrimer nanoconjuate containing a prostate specific cell permeation peptide, peptide therapeutic(s) and bifunctional chelator for PET imaging. Dr. Simanek's laboratory will make dendrimers that bear functional handles for conjugation with imaging agents (from Dr. Sun's laboratory) and proline-rich peptide as a therapeutic agent (from my laboratory).

We have designed different chemical modification of small peptide and characterized their *in vitro* biologic activities using several metastatic prostate cancer cell lines. Our data have shown the better activity of chemical modified peptide than prototype peptide. However, we did not observe any enhancement of activity after dendrimer conjugation, suggesting that peptide conjugation to dendrimer might have altered its structure. Nevertheless, we went ahead to examine its biologic activities *in vivo* using subcutaneous model and observed the tumorstatic effect of peptide at very high dosage, which may not be clinical applicable.

Overall, we conclude small peptide therapeutics remains a potential specific targeting agent. Nevertheless, there are still some issues regarding to drug delivery such as type of nanoparticle, chemistry of conjugation needed to be resolved in order to achieve an efficient delivery.

CHANGES/PROBLEMS

There is an issue of scale-up synthesis, which has delayed *in vivo* testing.

PRODUCTS

Publications, Conference papers, and Presentations

1. Lo, S., Kumar, A., Hsieh, J.T., Sun, X. (2013) Dendrimer nanoscaffolds for potential theranostics in prostate cancer. Mol. Pharm., 10:793-812.
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SPECIAL REPORTING REQUIREMENTS

N/A

Appendices

Figure 1 The effect of CSIV-81 on PC-3 tumor. One million cells were injected subcutaneously. When tumors became palpable, minupump containing CSIV-81 was implanted nearby tumor with a dosage of 10 mg/kg for 7 days delivery and tumor volume was determined at indicated time. Fold change was calculated using Day 0 (=1).

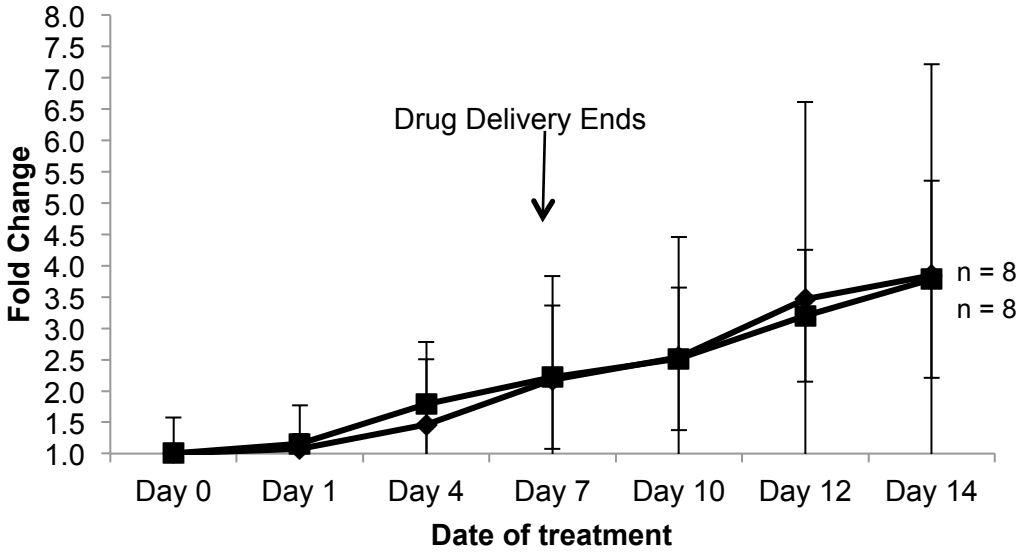

Figure 2 The effect of CSIV-81 on PC-3 tumor. One million cells were injected subcutaneously. When tumors became palpable, minupump containing CSIV-81 was implanted nearby tumor with a dosage of 50 mg/kg for 7 days delivery and tumor volume was determined at indicated time. Fold change was calculated using Day 0 (=1).

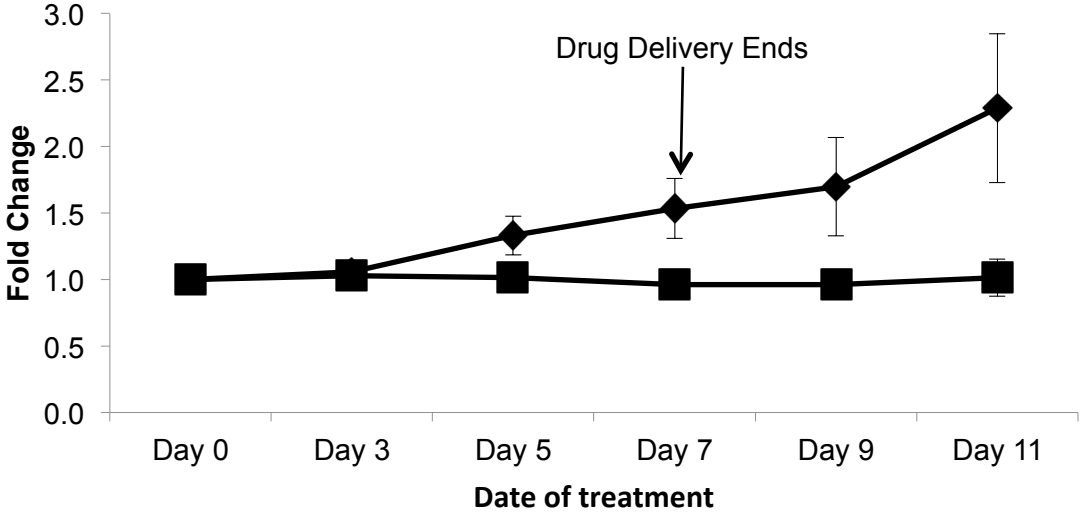

Figure 3 The *in vivo* target of CSIV-81 in PC-3 tumor. Three animals per group were injected with PC-3 ($1X10^6$ cells/site) subcutaneously. After tumor became palpable, minipump containing 10 mg/kg (Upper panel) or 50 mg/kg CSIV-81 (Lower Panel) was implanted nearby tumor site for 48 hrs and tumors were excised to prepare cells lysates subjected to western blot analyses.